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GREAT DEBATE
Ischaemic heart disease

Great debate: the universal definition of myocardial infarction is flawed and should be put to rest

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Abstract

Myocardial infarction (MI) is defined pathologically as myocardial cell death resulting from prolonged ischaemia. The clinical definition of this pathological process relies on clinical evidence of myocardial ischaemia and biomarker evidence of myocardial cell death. Cardiac troponins are the standard clinical biomarker for assessing cardiac cell death. Within the framework of the universal definition of myocardial infarction (UDMI), the definition of acute MI aims to guide clinicians to accurately diagnose and classify acute MI, and distinguish acute MI from other forms of myocardial injury in daily practice. In the latest (Fourth) UDMI, a major effort has been made to providing: (i) a stratified pathophysiology-informed framework for the classification of different MI types and (ii) an overview of the factors that should be considered for distinguishing MI from non-ischaemic myocardial injury. The development and implementation of the UDMI in its various iterations has intended to comprehensively define MI and not to provide an MI management guideline. It has resulted in major achievements. However, significant reservations have emerged among different stakeholders (*Graphical Abstract*) which form the basis of this 'Great Debate' manuscript.

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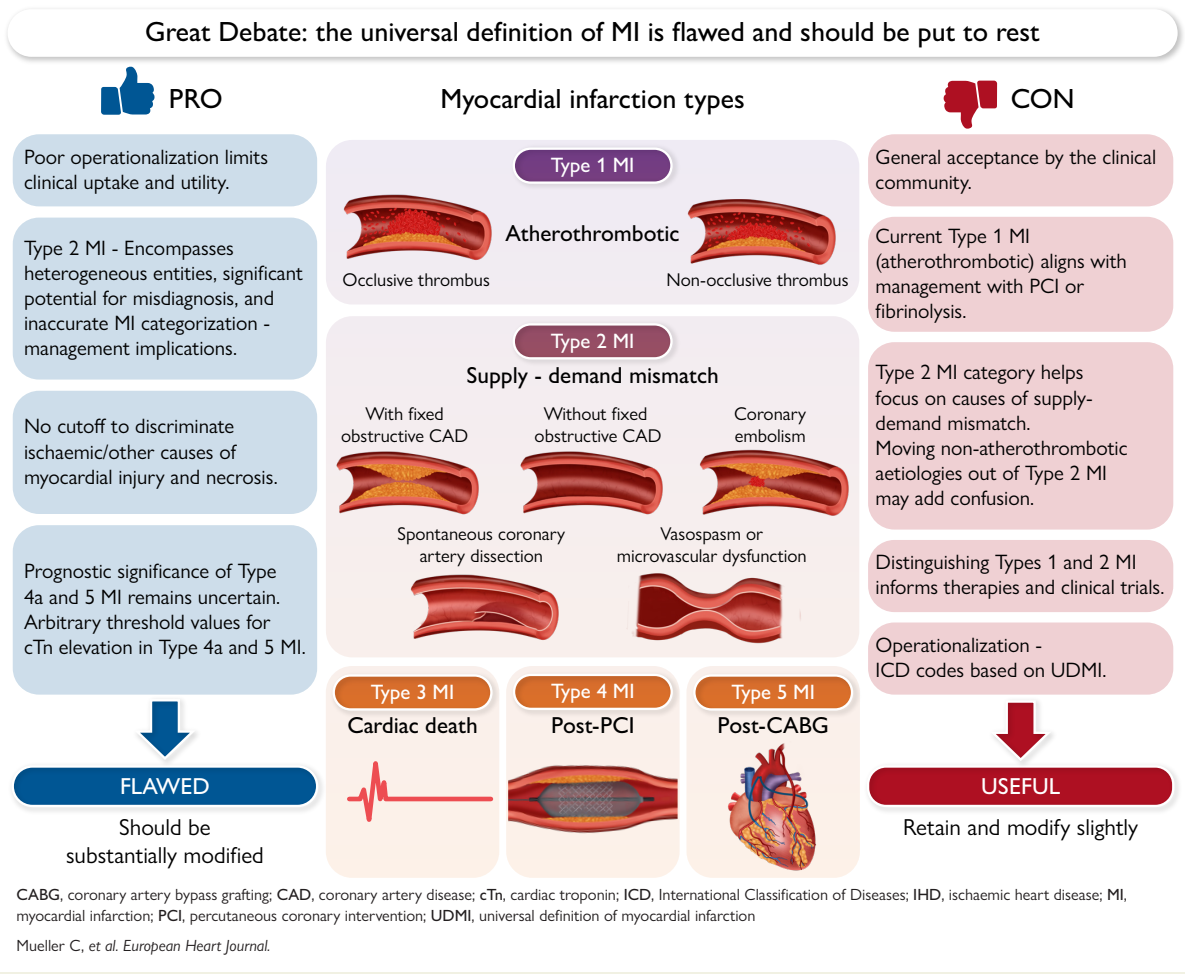
Graphical Abstract


Great Debate: the universal definition of MI is flawed and should be put to rest
PRO
Myocardial infarction types
CON
Poor operationalization limits clinical uptake and utility.
Type 2 MI - Encompasses heterogeneous entities, significant potential for misdiagnosis, and inaccurate MI categorization - management implications.
No cutoff to discriminate ischaemic/other causes of myocardial injury and necrosis.
Prognostic significance of Type 4a and 5 MI remains uncertain. Arbitrary threshold values for cTn elevation in Type 4a and 5 MI.
FLAWED
Should be substantially modified
Type 1 MI
Atherothrombotic
Occlusive thrombus
Non-occlusive thrombus
Type 2 MI
Supply - demand mismatch
With fixed obstructive CAD
Without fixed obstructive CAD
Coronary embolism
Spontaneous coronary artery dissection
Vasospasm or microvascular dysfunction
Type 3 MI
Cardiac death
Type 4 MI
Post-PCI
Type 5 MI
Post-CABG
General acceptance by the clinical community.
Current Type 1 MI (atherothrombotic) aligns with management with PCI or fibrinolysis.
Type 2 MI category helps focus on causes of supply-demand mismatch. Moving non-atherothrombotic aetiologies out of Type 2 MI may add confusion.
Distinguishing Types 1 and 2 MI informs therapies and clinical trials.
Operationalization - ICD codes based on UDMI.
USEFUL
Retain and modify slightly
CABG, coronary artery bypass grafting; CAD, coronary artery disease; cTn, cardiac troponin; ICD, International Classification of Diseases; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; UDMI, universal definition of myocardial infarction
Mueller C, et al. European Heart Journal.

This graphical illustration summarizes the arguments put forward in this great debate by the PRO and CONTRA authors, respectively. ECG, electrocardiogram; CABG, coronary artery bypass grafting; cTN, cardiac troponin; HScTn, high sensitivity cardiac troponin; ICD, International Classification of Diseases; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; UDMI, universal definition of myocardial infarction.

Keywords Myocardial infarction • Universal definition of MI • Acute coronary syndrome • Myocardial injury • Myocardial infarct types

Introduction

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The universal definition of myocardial infarction (UDMI) has resulted in major achievements including the identification of atherothrombotic and non-atherothrombotic causes of MI, classification of periprocedural MI types, provision of standardized definitions for clinical and epidemiological research as well as informing the establishment of specific codes for MI subtypes in the International Classification of Diseases (ICD) version 10. However, questions have emerged in recent years among different stakeholders regarding the goals and clinical usefulness of the UDMI, which are addressed in the present 'Great Debate'.

Do we need a UDMI? The UDMI aims to guide clinicians to accurately diagnose and classify acute MI. MI is defined pathologically as myocardial

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cell death resulting from prolonged ischaemia. The clinical definition of this pathological process relies on clinical evidence of myocardial ischaemia and biomarker evidence of myocardial cell death. Cardiac troponins are the standard clinical biomarker for assessing cardiac cell death.[1–4]

How does one follow the pathologic definition of MI in clinical practice? In the latest (Fourth) UDMI,[1] efforts were made to providing: (i) a stratified pathophysiology-informed framework for the classification of different MI types and (ii) an overview of the factors that should be considered for distinguishing MI from non-ischaemic myocardial injury. Several mechanisms, in addition to myocardial injury and necrosis, have been suggested to be responsible for troponin release including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, and the formation and release of membranous vesicles.[5,6] However, despite the potential role of these mechanisms, there are no strong experimental data that indicate that when troponin is released, cell death does not occur. Even brief episodes of ischaemia can cause cell death and troponin release. Whether incorporating imaging (echocardiogram) evidence of myocardial necrosis to the definition may improve diagnosis and clinical management is another important discussion point. Would such adjunctive imaging tool be immediately available in the vast majority of cases and would it be cost-effective to implement diagnostic algorithms based on echocardiography?

Another issue here is whether or not coronary artery disease is essential for a diagnosis of MI (MI with no obstructive coronary artery disease—'MINOCA'—would not be an MI if it was). Type 1 MI is currently defined as an acute event resulting from atherosclerotic plaque rupture, fissuring and/or erosion leading to intraluminal thrombus formation, decreased myocardial blood flow, and ensuing myocyte necrosis. This can occur in the presence of coronary atherosclerosis of varying luminal severity. However, supply–demand mismatch resulting from a primary reduction in epicardial coronary flow leading to myocardial ischaemia and injury may also occur in patients without obstructive atherosclerotic coronary artery disease due to coronary vasospasm, non-atherosclerotic coronary dissection, or coronary embolism. These patients (type 2 MI) often present with symptoms and electrocardiographic features that are indistinguishable from atherothrombotic MI. Guidelines recommend specific treatment based on clinical, angiographic, and functional data in addition to biomarkers and these considerations have stimulated proposals to redefine Type 1 MI.[7,8] Type 2 MI is considered to result from a supply–demand mismatch arising from both coronary (e.g. epicardial flow-limiting stenosis without acute atherothrombosis, coronary vasospasm, coronary microvascular dysfunction, and non-atherosclerotic coronary dissection) and non-coronary (e.g. tachyarrhythmia, hypoxaemia, hypotension, hypertensive crisis, and anaemia) pathologies. Each of these mechanisms requires distinct treatments and is associated with differing clinical outcomes. This inherent heterogeneity has been suggested to limit the clinical utility of this diagnostic category.[9,10] Measurement of biomarkers of ischaemia, endothelial dysfunction, microvascular dysfunction, and haemodynamic stress has been shown to add only marginally to distinguishing myocardial injury and necrosis in the clinical setting.[11–14] As for obstructive coronary artery disease, Type 2 MI, epicardial coronary atherosclerosis may be demonstrated in patients with Type 2 MI but it is often not flow limiting,[15] highlighting the potential importance of disorders of the coronary microcirculation and/or vasomotion as causes of Type 2 MI and that obstructive coronary artery disease is not essential for the diagnosis of MI. Clinicians have questioned the clinical utility of this diagnostic category given the lack of evidence base informing how the spectrum of Type 2 MI should be managed or whether management leads to improved clinical outcomes.[14] The UDMI is not meant to be a management guideline, but it nevertheless informs management strategies and also stimulates the search for effective, specific treatments for the newer MI categories. Are changes in the UDMI regarding Type 2 MI needed to help patient management or should the UDMI remain unchanged to remind clinicians of the variety of mechanisms able to trigger myocardial ischaemia/necrosis? Similarly, questions have emerged as to the clinical relevance of MI categories 4a and 5, which have been adopted for endpoint adjudication in clinical trials but questioned by clinicians who consider troponin cut-offs for diagnosis of Type 4a and type 5 MIs to be arbitrary and not evidence-based. Cardiac troponin measurements are not recommended in revascularization guidelines and are variably performed after coronary revascularization. Should this issue lead to a change in the UDMI?

Finally, despite major clinical benefits resulting from the introduction of the UDMI, its operational utility in clinical practice is currently a matter of debate among clinicians, academics, and triallists, with new approaches for defining acute MI[16] being proposed to make the UDMI more clinician friendly and operationally useful. The question, however, emerges as to what extent the operationalization of the definition should be part of the UDMI goal. Some clinicians suggest that drastic changes are necessary, as the UDMI is excessively complex and results in limited and inconsistent implementation, particularly considering the diversity of healthcare settings, systems, regulatory frameworks, and resource availability in which patients are assessed. However, can the UDMI be modified to cater for currently unmet needs without having to redo all the existing literature?

The areas briefly mentioned in this introduction form the basis of the present Great Debate.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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Pro

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The universal definition of myocardial infarction (UDMI) has, since its first iteration more than 20 years ago,[1] enabled the use of standardized diagnostic criteria for myocardial infarction (MI) in routine clinical practice (*Figure 1*) and contributed to improve the management of millions of MI patients worldwide. In this section of the Great Debate, we argue, however, that the latest iteration, the 2018 'Fourth Universal Definition of Myocardial Infarction', which defines seven distinct subtypes of MI (type 1, type 2, type 3, type 4a, type 4b, type 4c, and type 5)[2] may be overly complex and lead to inconsistent or and often incorrect decisions in clinical practice and research, as recently suggested by other authors.[3–5] While MI, defined as a condition wherein acute cardiomyocyte injury results from myocardial ischaemia, can now be easily detected and quantified in clinical practice by an acute rise in systemic cardiac troponin (cTn) concentration above the upper limit of normal (ULN), accurately identifying myocardial ischaemia and distinguishing it from other causes of cTn elevation is often difficult. Moreover, we argue that among the seven UDMI MI subtypes, types 2, 4, and 5 are flawed and should be revised. In addition, we propose a slight modification to type 1. Our concerns are mainly based on the impact that the UDMI may have on real-life patient management.

To illustrate our primary critique, we invite the reader to consider the general validity of the following statements: MI is a potentially life-threatening condition, demanding immediate ECG rhythm monitoring. Those with ST-segment elevation MI should undergo immediate coronary angiography, while those with non-ST-segment elevation MI should undergo early angiography.[6,7] Additionally, MI patients are typically recommended to be managed according to established guidelines.[7] Importantly, however, when using the term MI, physicians think of type 1 MI, caused by primary coronary flow reduction resulting from coronary atherothrombosis, as the cause of ischaemia. However, the UDMI encompasses many other MI subtypes that have little in common with type 1 MI, regarding management and clinical outcomes.

Type 2 MI

Type 2 MI, defined as a supply–demand mismatch unrelated to coronary atherothrombosis leading to myocardial ischaemia and necrosis can be triggered by different mechanisms including spontaneous coronary artery dissection (SCAD), coronary embolism, coronary spasm, tachy- and bradyarrhythmias, severe hypertension, respiratory failure, hypotension, or severe anaemia (*Figure 2*). Type 2 MI may thus have different clinical outcomes, may require different treatments and differs in many ways from type 1 MI. The use of the term 'MI' for these different conditions results misleading for many, and can potentially harm patients, as physicians commonly associate 'MI' with type 1 MI. Type 1 MI requires aggressive antithrombotic therapy and coronary revascularization) whereas treatment for type 2 MI is based on treating the trigger). Physicians may inadvertently administer treatments intended for type 1 MI to type 2 MI patients.[7,8] Inappropriate coding of MI type can also occur, which has implications for accurate epidemiological data acquisition.

The current classification of type 2 MI is problematic for the following reasons: first, mechanisms that cause an oxygen supply–demand imbalance differ markedly in patients with type 2 MI due to a non-atherothrombotic mechanism (SCAD, coronary embolism, and coronary vasospasm), which account for ~7% of all type 2 MIs,[9] vs those triggered by brady- or tachycardia, hypo- or hypertension, anaemia, or hypoxemia. Second, diagnosis in the latter depends on fully characterizing the clinical condition and although in some cases non-invasive imaging like echocardiography may be used[10] coronary imaging (invasive or non-invasive) is rarely needed upon arrival unless ischaemic symptoms persist despite correction of the acute trigger or if regional wall motion abnormalities are detected on imaging. It is unlikely that the initial management of a patient with severe bleeding leading to anaemia and type 2 MI would differ that in a patient with severe bleeding and anaemia but without Type 2 MI as in both cases, the clinical priority is to control the bleeding. This is further supported by the fact that no study has shown that identifying type 2 MI improves management or outcomes. Third, from a practical standpoint, the UDMI flowchart, which early on separates acute ischaemia from non-ischaemia, incorrectly assumes that in clinical practice, we have sensitive and specific symptoms, signs, ECG characteristics or biomarkers differentiating myocardial ischaemia from other causes of injury such

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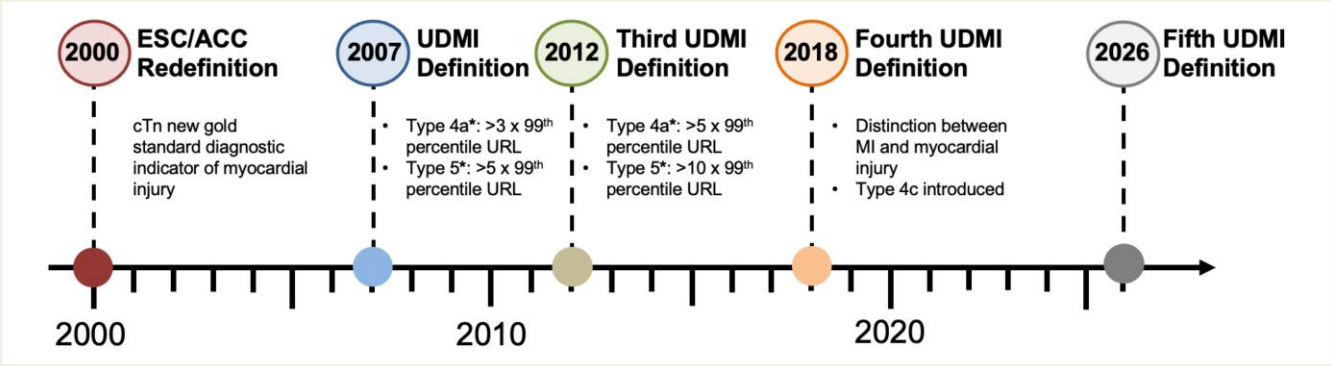

Figure 1 Timeline of the universal definition of myocardial infarction. *With at least one of the following: (*A*) new ischaemic ECG changes (only for type 4a); (*B*) development of new pathological Q waves; (*C*) imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology; or (*D*) angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. UDMI, universal definition of myocardial infarction; ESC/ACC, European Society of Cardiology/American College of Cardiology; URL, upper reference limit; MI, myocardial infarction; T2MI, type 2 myocardial infarction; cTn, cardiac troponin; CAD, coronary artery disease

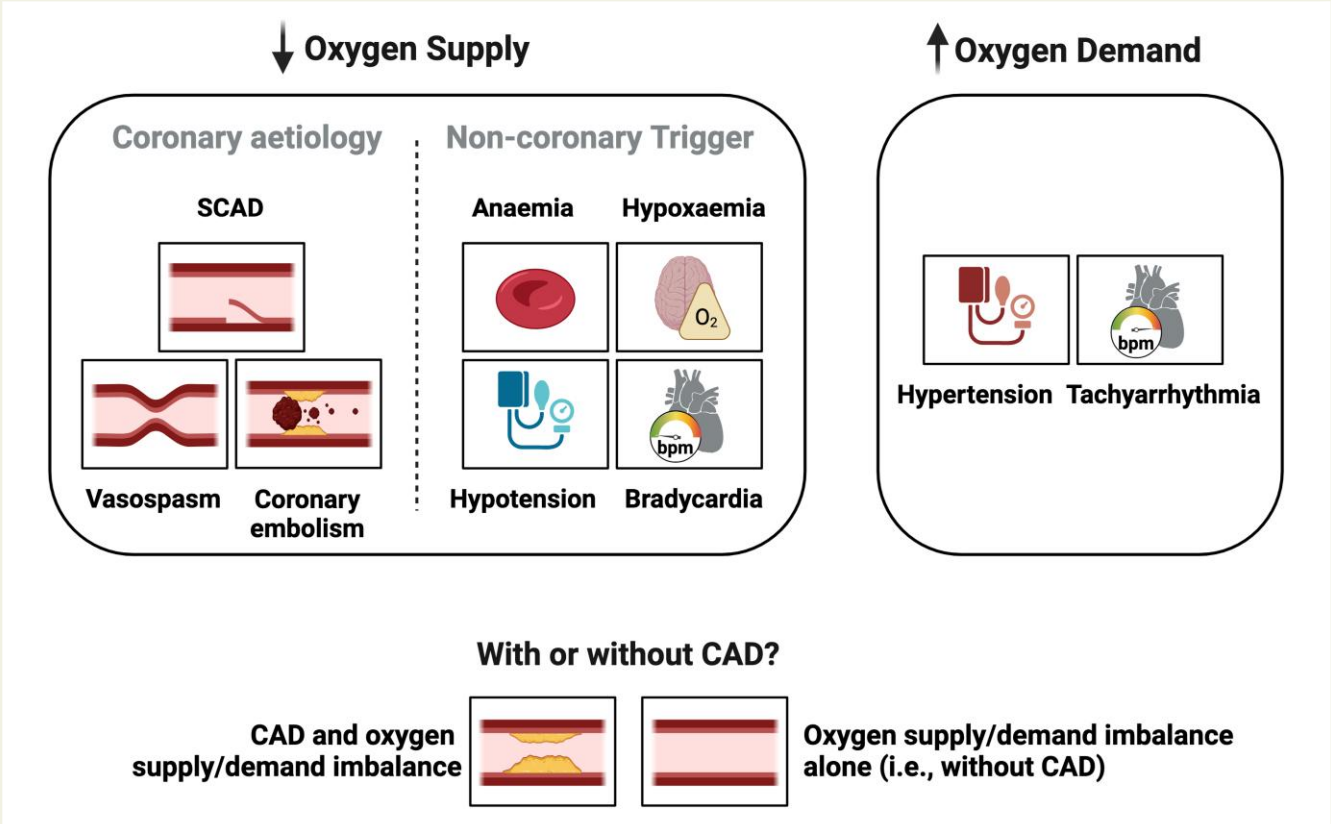

Figure 2 Main mechanisms leading to type 2 MI. A reduction in oxygen supply or increase in oxygen demand can lead to type 2 MI. Most cases of type 2 MI are triggered by non-coronary aetiologies. T2MI can occur in patients with coronary artery disease or without coronary artery disease. MI, myocardial infarction; SCAD, spontaneous coronary artery dissection; CAD, coronary artery disease

as myocarditis or Takotsubo cardiomyopathy. Fourth, left ventricular hypertrophy due to severe aortic stenosis or hypertrophic cardiomyopathy can also result in myocardial ischaemia, yet its management is unrelated to that of myocardial infarction.

Taking all the above together, we propose that the term Type 2 MI should be restricted to the coronary aetiologies, as the initial diagnostic work-up resembles that of type 1 MI and includes early coronary angiography for the reliable diagnosis and possible treatment (*Figure 3*). For

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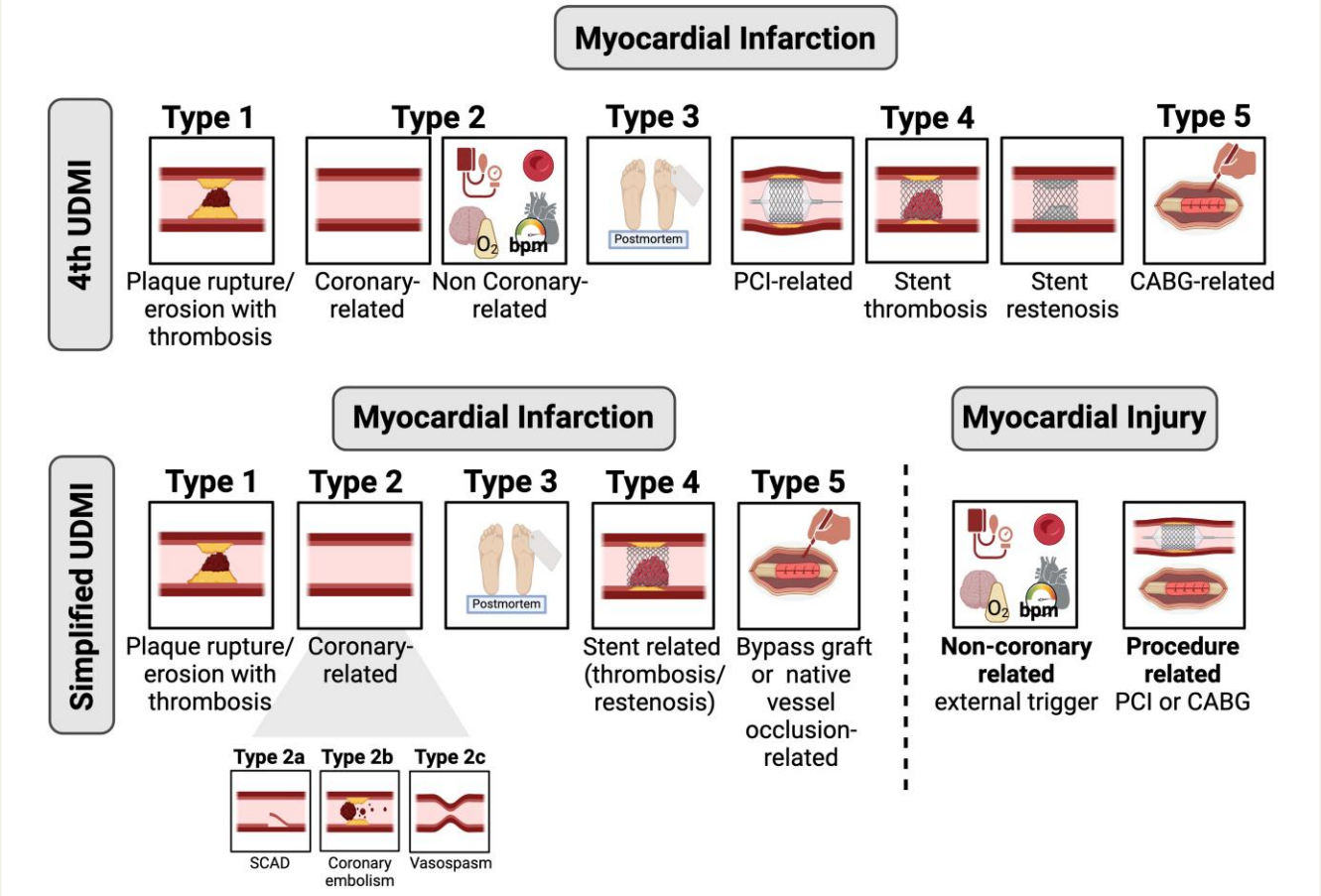

Figure 3 Proposed reclassification for the universal definition of myocardial infarction. Type 1 MI (plaque rupture/erosion with thrombosis) would remain classified as type 1 MI. Type 2 MI, however, would be restricted to coronary aetiologies (SCAD, coronary embolism, and vasospasm) since the initial diagnostic work-up closely resembles that of type 1 MI and includes early coronary angiography for the reliable diagnosis and possible treatment. In contrast, the remaining non-coronary aetiologies would no longer fall in the umbrella term of type 2 MI. instead, they would be reclassified as myocardial injury non-coronary related, reflecting the fact that their management should focus primarily on addressing the underlying trigger rather than adhering to a myocardial infarction treatment paradigm. Not distinguishing between acute myocardial injury and type 2 MI in these cases may help shift attention towards the appropriate causal treatment. Type 3 MI would remain unchanged. Type 4a MI would be redefined as myocardial injury procedure-related, while type 4b and type 4c MIs—both stent-related events—would continue to be classified as type 4 MI. Finally, type 5 MI would be restricted to cases with documented acute occlusion of a bypass graft or native vessel, whereas all other post-CABG cases would fall under the category myocardial injury procedure-related MI. UDMI, universal definition of myocardial infarction; SCAD, spontaneous coronary artery dissection

the remaining systemic causes of supply–demand mismatch, avoiding the term MI and not distinguishing between acute myocardial injury or type 2 MI seems preferable to deviate the attention from causally treating the respective trigger. Several large studies showing that patients labelled as type 2 MI or acute myocardial injury have comparable long-term outcomes support our suggestion.[8,11–14] Importantly, a recent Delphi survey involving an international group of experts, highlighted the need for a revision of the current type 2 MI definition.[15] Furthermore, there is very limited, if any, pathological or histopathological evidence that the events that are currently considered triggers of Type 2 MI actually cause ischaemic cardiomyocyte death. If despite all these arguments type 2 MI is to be retained in future iterations of the UDMI, subclassifying MI according to the presence or absence of coronary artery disease (CAD) should be considered, for prognostic and treatment reasons (i.e. secondary prevention).[9,11,12,16]

To better highlight what we consider flaws related to the definition of type 2 MI and implications for the diagnosis and management of patients, five clinical scenarios are depicted in *Figure 4*. In the first three cases, all non-coronary related, the initial priority was the management of the acute illness, while in the last two, coronary related, a completely different work-up and management (i.e. anticoagulation therapy, coronary angiography, and possible revascularization) is required.

Type 4 and Type 5 MIs

Type 4 and type 5 MIs result from periprocedural complications: type 4a with percutaneous coronary intervention (PCI), type 4b with stent/scaffold thrombosis, type 4c with stent restenosis, and type 5 with coronary artery bypass grafting (CABG).[2] These subgroups that were introduced and updated in the third and fourth iterations of the UDMI (*Figure 1*),[2,17] are rarely considered in clinical practice. Type 4a and Type 5 MIs have sparked considerable debate among cardiologists and cardiac surgeons. Several criticisms have been made to the current

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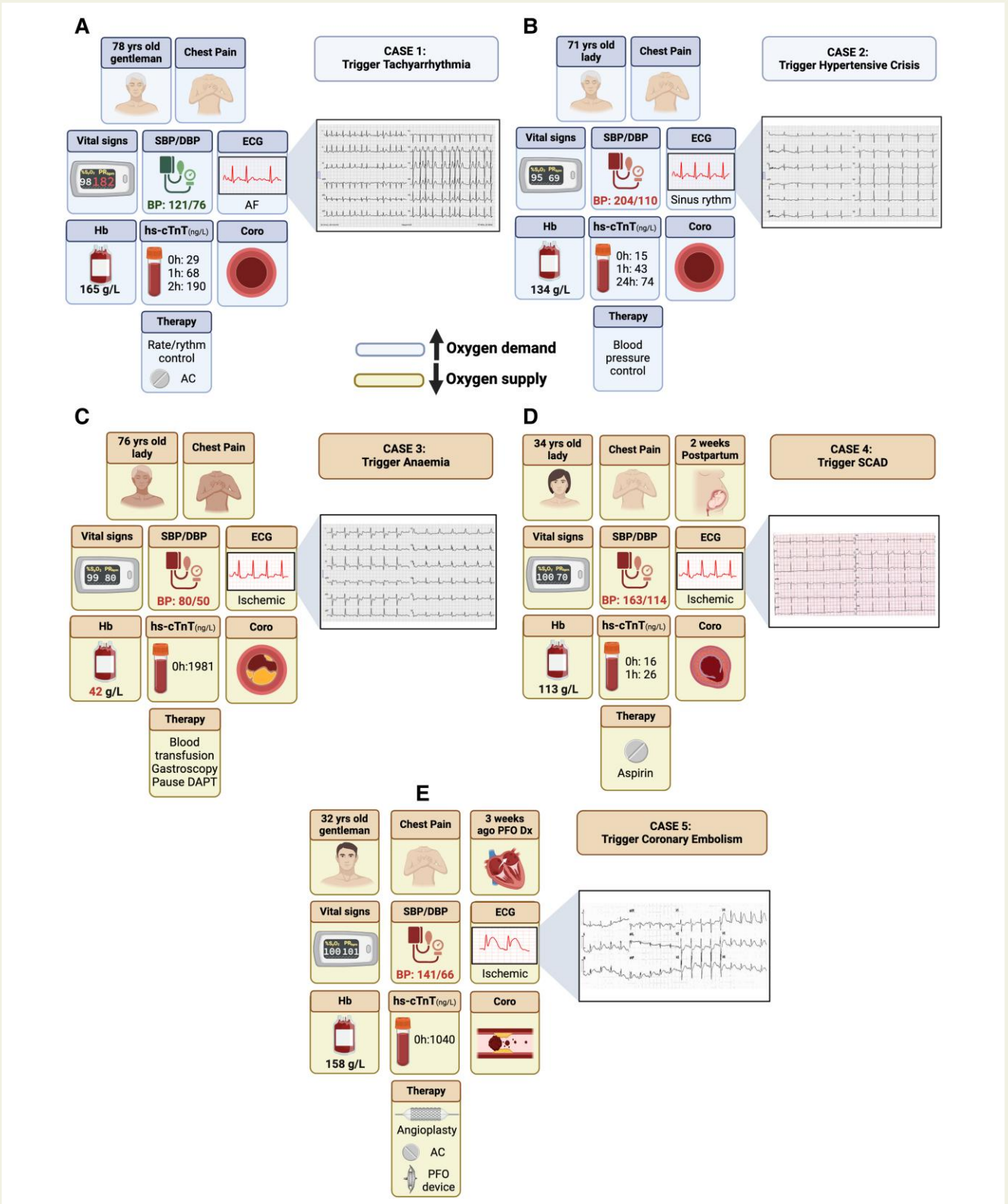

Figure 4 Four clinical scenarios for type 2 MI. (*A*) Increased oxygen demand in the context of a tachyarrhythmia (182 b.p.m.) in a 78-year-old gentleman; (*B*) increased oxygen demand in the context of a hypertensive crisis (204/110 mmHg) in a 71-year-old lady; (*C*) reduced oxygen supply in the context of anaemia (Hb 42 g/L) in a 76-year-old lady; (*D*) reduced oxygen supply in the context of a spontaneous coronary artery dissection in a 34-year-old lady, two weeks after childbirth; and (*E*) reduced oxygen supply in the context of a coronary embolism (distal occlusion of a small marginal artery) in a 32-year-old gentleman, three weeks after a patent foramen ovale was diagnosed. BP, blood pressure; ECG, electrocardiogram; AF, atrial fibrillation; HB, haemoglobin; hs-cTnT, high sensitivity cardiac troponin T; AC, anticoagulant; PFO, patent foramen ovale

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7definitions of type 4 and type 5 MIs such as the ill-defined purpose of the definition, the arbitrary threshold values for cTn elevation, uncertainties regarding the pathogenesis of such elevations, controversy as to whether type 4 and 5 MIs would need to have prognostic impact to justify its use.

High sensitivity cTn raises in many patients after PCI and the procedure is responsible for this elevation in most cases with only a minority being non-ischaemic in origin (e.g. severe hypotension, severe hypertension, or major prolonged arrhythmia). The reaction of the interventional community to the findings of prospective studies showing that most contemporary PCIs result in cTn elevations above the ULN[18–21] was to modify the diagnostic criteria for type 4a MI to artificially reduce its prevalence. Based on the UDMI these events should be labelled 'periprocedural MIs' and could represent both an outcome measure and a quality assurance criterion to improve PCI technology. Of interest and a reflection of the usefulness or lack of it in clinical practice, while the current UDMI requires an increase in cTn greater than five times the ULN in conjunction with either angiographic evidence of a major complication (i.e. occlusion of a side branch, new ischaemic ST-segment changes, or pathological Q waves) or imaging evidence of new loss of viable myocardium, the Academic Research Consortium-2[22] and the Society for Cardiovascular Angiography and Interventions[23] require an increase in cTn concentration ≥ 70 times the ULN. Hence, the cut-off for PCI myocardial injury to be labelled MI must be 70 times higher than that required for spontaneous MI. Most clinicians would agree that moving the goalpost in such a way is not a reasonable option. However, this highlights the fact that the UDMI is just a definition and not a guideline for clinical management. The cut-offs for type 4a MI UDMI definition were suggested for elective PCI procedures. Discussions regarding cut-offs to use in primary PCI is an even more complex issue.

The definition of type 5 MI after CABG requires similar considerations, albeit the pathophysiology here is more heterogenous, with some of the perioperative cardiomyocyte injury being ischaemic in origin (e.g. reperfusion injury, thrombosis, or graft failure) and some non-ischaemic origin (e.g. cannulation, cardioplegia, cardiac manipulation, arterial injury, or tachyarrhythmia).[24] Similar to PCI, the definition of periprocedural MI for CABG was arbitrarily modified. A rise in cTn exceeding 500 times the ULN in patients with ST-segment depression would be labelled type 5 MI only if new pathological Q waves develop, or if coronary angiography shows new graft or native coronary occlusion, or if imaging techniques show new loss of viable myocardium.[2]

One of the detrimental consequences of setting arbitrary thresholds to define type 4a and 5 MIs is for example the difficulty to interpret the results of clinical trials comparing PCI vs CABG, which include periprocedural MI in their composite endpoints.[25–29] This has unfortunately prevented accurate comparisons between studies, due to variable definitions of type 4 and type 5 MIs in the trials.[26–30] Consequently, with the current definition, only death, stroke, and spontaneous MI remain as unbiased relevant cardiovascular endpoints for comparison. In addition, hospitalization due to heart failure, as well as patient-centred outcomes (e.g. quality-of-life measures and cognitive impairment) may also be considered, as these reflect outcomes of importance.

Taken all the above together, we believe that the definition of type 4a and type 5 MIs should be reconsidered. This process should involve general cardiologists, interventionalists, cardiac surgeons, biostatistician/epidemiologists, patients, and all other relevant stakeholders to agree on clinically relevant definitions of these MI types that can be widely and effectively applied in clinical practice and research.

In addition to the ongoing discussion about the extent of acute myocardial injury required to define periprocedural myocardial infarction, we propose simplifying the MI subtype classification by retaining only acute stent thrombosis (4b) and stent restenosis (4c) as type 4 MI and restricting type 5 MI to cases with documented acute occlusion of a bypass graft or native vessel (*Figure 3*).

In summary, major uncertainties revolve around the clinical usefulness of type 2, type 4, and type 5 MIs, which may even harm patients. A substantial revision of the UDMI seems mandatory—in our view—to make it useful in clinical practice. The suggested changes would enhance the alignment of diagnosis and management across the whole spectrum of MI and thus reduce existing diagnostic uncertainties and foster widespread adoption in everyday clinical practice. We acknowledge that the modification of International Classification of Diseases codes may involve a significant time investment, but administrative challenges should not deter us from potentially improving the diagnosis and management of a life-threatening condition like MI.

Acknowledgements

Figures 2–4 were created with BioRender.com.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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I am delighted to have the opportunity to debate the moot 'The Universal Definition of Myocardial Infarction (UDMI) is flawed and needs to be put to rest.' I will respond to each of the points in the PRO section and talk about the future and other proposals for modification of the UDMI. The PRO team argues that seven subtypes of MI may be overly complex and lead to inconsistent and often incorrect decisions in clinical practice and research. I will argue that the UDMI is well accepted in clinical practice and has been used in multiple clinical trials.

I don't deny that MI is a potential life-threatening condition, but I don't agree that all patients with ST elevation of myocardial infarction (STEMI) should have *immediate* angiography. What about administration of fibrinolysis in a non-PCI-capable hospital? Nor do I agree that all non-STEMI patients should have *early* coronary angiography. The ESC guidelines recommend a selective invasive approach for patients without very high or high risk features of non-ST elevation of myocardial infarction (NSTEMI).[1]

They also argue that the use of the term MI for type-2 MI is misleading for many and potentially may harm patients. But as pointed out in the introduction, MI is defined pathologically as myocardial cell death resulting from prolonged ischaemia. The clinical definition of this pathological process relies on clinical evidence of myocardial ischaemia and biomarker evidence of myocardial cell death. Thus, the seven types

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of MI in the UDMI all fulfil this definition and should not be called myocardial injury. The PRO team raise issues of inappropriate coding and physicians inadvertently administering wrong treatments. Surely this would be unrelated to a definition and related to inappropriate behaviour and perhaps coders and physicians not reading and understanding the UDMI.

Separation of ischaemia from non-ischaemia

It is very important to separate myocardial injury from MI and this is done based on whether clinical ischaemia is present or not as defined in the UDMI. Experienced physicians do this every day and probably do it very well. The presence of ischaemia is critical to the diagnosis of MI and ischaemia or ischaemic complications are required in all the definitions of the types of MI including Type-4a (*Table 1*).

The Pro group comment correctly that left ventricular hypertrophy can result in ischaemia. If, however, there is myocyte necrosis as indicated by troponin elevation then it becomes a Type-2 MI and requires investigation and management.

Evidence of ischaemic cardiomyocyte death in Type 2 MI

There are multiple causes of troponin elevations[2] as listed in *Table 2*. However, current data indicate that all causes of troponin elevation are associated with myocardial cell death. All Type-2 MIs have coronary necrosis *ipsi facto* as troponins are raised, thus meeting the pathological definition of MI.

Type-4 MI and Type-5 MI definitions

The UDMI includes the need for an ischaemic complication for both Type-4a and -5 MIs and not just an elevation of troponin. This is similar to the need to have ischaemic aetiologies for Type-1 and Type-2 MIs. Pragmatically, we must have a definition that identifies the threshold of injury intrinsic to the procedure and values above that to make the diagnosis of MI.

In the UDMI, the diagnosis of Type-4a MI (PCI related) has been based on the presence of both ischaemia and complications including decreased TIMI flow, loss of a side branch, loss of collaterals, embolism, or dissection. The UDMI requires a five-fold threshold for hs-troponin with a normal baseline, supported by spline curves of increasing risk with increasing troponin levels.[3,4]

During CABG, numerous factors can lead to background periprocedural myocardial injury as part of an uncomplicated procedure (*Table 3*).[5] That is why the threshold for myocardial injury is and should continue to be higher for cardiac surgery than for PCI.[3] The UDMI diagnostic criteria are summarized in *Table 4*.

The PRO proposal takes away ischaemic complications from Type-4a MI and moves Type-4a to procedural myocardial injury. They don't define the rise of hs-troponin to be required to fulfil their definitions. Their proposal also does away with the development of Q waves in Type-5 MI. The presence of Q waves has been used for many years by clinicians and is in the definition of clinically relevant MI[6] and the Academic Research Consortium ARC-2[7] definition for clinical trials. The later definition requires for both PCI and CABG procedures hs-troponin levels rising to ≥70 times the manufacturer-recommended upper reference limit (URL), or ≥35 times the ULN with new pathologic Q waves in ≥2 contiguous leads.[7] ARC-2 also recommends the need for either flow-limiting angiographic complications, or new substantial loss of myocardium on imaging.[7] The PRO group proposal keeps the same

Table 1 Criteria required for the identification of Type-4a MI

1	New ischaemic ECG changes; ST depression↓ 0.5 mm, ST elevation ↑1.5 mm in females, ↑2 mm in males, new LBBB as for Type-1 MI
2	Development of pathological Q waves
3	Elevated cellular troponins five times above normal baseline levels

Table 2 Pathobiological classification of potential mechanisms causing troponin elevations

Type 1	Myocyte necrosis
Type 2	Apoptosis
Type 3	Normal myocyte turnover
Type 4	Cellular release of proteolytic troponin degradation products
Type 5	Increased cellular wall permeability
Type 6	Formation and release of membranous blebs

Table 3 Causes of myocardial injury with coronary artery bypass

1	Direct myocardial trauma from suture placement or manipulation of the heart
2	Dissection out of coronary arteries
3	Global or regional ischaemia related to inadequate intra-operative cardiac protection
4	Microvascular events related to reperfusion
5	Myocardial injury induced by oxygen free radical generation
6	Failure to reperfuse areas of the myocardium that are not subtended by graftable vessels

Table 4 Universal definition of myocardial infarction with coronary artery bypass grafting criteria

A 10-fold URL elevation in hs-troponin from a normal baseline
Either (i) New pathological Q waves or LBBB OR
(ii) Angiographic documented new graft or new native coronary artery occlusion OR
(iii) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

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definitions as the UDMI for type 4b (acute stent thrombosis) and type 4c (restenosis).

The concept of a definition of MI requiring prognostic data as proposed by many interventionists and discussed by the PRO group is an anathema. Prognosis varies depending upon the outcomes and timepoints chosen and depends on whether there was a potential beneficial intervention such as PCI. It has been suggested that it is possible that the CABG and PCI definitions may have been distorted by those with vested interests, even though the groups referenced above have reported their conflicts of interest.[3]

Importance of cardiovascular death as an outcome

The PRO group argues that when comparing PCI and CABG in clinical trials that only death, stroke, and type 1 MI remain as unbiased, relevant cardiovascular endpoints. They don't mention cardiovascular death as a desired outcome. Total death includes non-cardiovascular cause such as cancer and infections, and apart from chance cannot be affected by a treatment. Cardiovascular death, on the other hand, is specific to the effects of a treatment.[8]

Medical therapy for Type-2 MI

There have been no randomized clinical trials (RCTs) of penicillin or parachutes and yet both should and clearly are used. In my view, a similar approach should be used for the management of Type-2 MI. In the absence of RCTs, I think it is reasonable to manage patients with type 2 MI the same as patients with type 1 MI given that the effect on the myocardium is the same. The cause of the supply/demand imbalance should be treated, and patients with spontaneous coronary artery dissection (SCAD), vasospasm, and embolism require individual approaches. Patients with Type-2 MI should be monitored for arrhythmias. Beta-blockers should be given if the left ventricular ejection fraction is decreased and the '4 pillars' of heart failure treatment should be prescribed (beta blockers, angiotensin receptor and a neprilysin inhibitors, spironolactone, and a SGLT-2 inhibitor) if heart failure is present. Patients should attend cardiac rehabilitation and receive treatments for dyslipidaemia and hypertension, nutrition and exercise advice, and influenza vaccination, as appropriate.

On the basis of the Myocardial Ischaemia and Transfusion (MINT) trial,[9] the 2025 ACC/AHA guidelines for management of patients with acute coronary syndromes give a 2b recommendation 'In patients with ACS and acute or chronic anaemia, blood transfusion to achieve a haemoglobin level ≥ 10 g/dL may be reasonable to reduce cardiovascular events.'[10] In the MINT trial, 1460 patients with Type-1 and 1955 patients with Type-2 were randomized.[11] The primary outcome of death or MI was observed in 16% of Type 1 MI and 15.4% of type 2 MI patients and the test for a differential effect of transfusion strategy by MI type was not statistically significant ($P_{interaction} = .16$). Thus, the guideline recommendations apply to both Type-1 and Type-2 MIs.

Need for a coronary angiogram

The pro group states that all patients with STEMI should have an *immediate* angiogram while those with non-STEMI should undergo *early* angiography. Coronary angiography including CTCA is not required to assist in the diagnosis of MI. Also, patients may have MI with non-obstructive coronary arteries (MINOCA) which may occur in up to 10% of cases of MI.[12,13]

The diagnosis of MI is not predicated on whether there is coronary artery disease (CAD) or not and angiography is not recommended in the Fourth UDMI for the diagnosis of MI. However, angiography is important to identify causes of MI such as stent thrombosis, spasm, and dissection.

Need for an echocardiogram

One of the UDMI criteria for the diagnosis of MI is echocardiographic findings of loss of myocardial viability or new wall motion abnormalities. Therefore, MIs will be missed if other criteria are not present, and an echocardiogram (ECG) is not done. An ECG is important when the troponin values are ambiguous and to define other cardiac pathology such as Takotsubo syndrome, right ventricular function, which may indicate pulmonary embolism, mechanical complications (VSD, rupture, mitral regurgitation) valvular function, the presence of thrombus, and to assess the left ventricular ejection fraction. Measurement of ejection fraction is very important to determine prognosis and management. It is notable that none of the cases that the pro side presented had an ECG. The idea of getting echoes ubiquitously will still be relatively expensive if widely applied.

Achievements of the universal definition of MI group

The big change in 2007 was the introduction of a whole new class of MIs (Type-2, 3, 4a, 4b, and 5) (*Table 5*).[14]

Consensus with the universal definition of MI

Reviewers involved in the formal review process sent ~80 comments with 30 further comments replying to the initial responses from the UDMI group. In addition, there were over a thousand other comments

Table 5 Achievements of the universal definition of myocardial infarction group

1	In the third definition (2007),[5] six types of infarctions were introduced.
2	In 2012, the UDMI[27] incorporated high sensitivity troponin assays.
3	In the fourth UDMI (2018),[28] SCAD was changed from Type-1 to Type-2 as it usually is not atherothrombotic and there is oxygen supply/demand mismatch with decreased supply due to thrombus formation.
4	Type 4c was introduced as MI due to stent or angioplasty restenosis.
5	Chest pain was taken out of type 4a MI (periprocedural PCI) as it is ubiquitous and is not helpful to distinguish MI from non-MI.
6	More detailed consideration of myocardial injury.
7	Included silent MIs.
8	The ESC guidelines[1] and the recent ACC/AHA guidelines[10] for the management of patients with ACS use the UDMI to define Type-1 MI.

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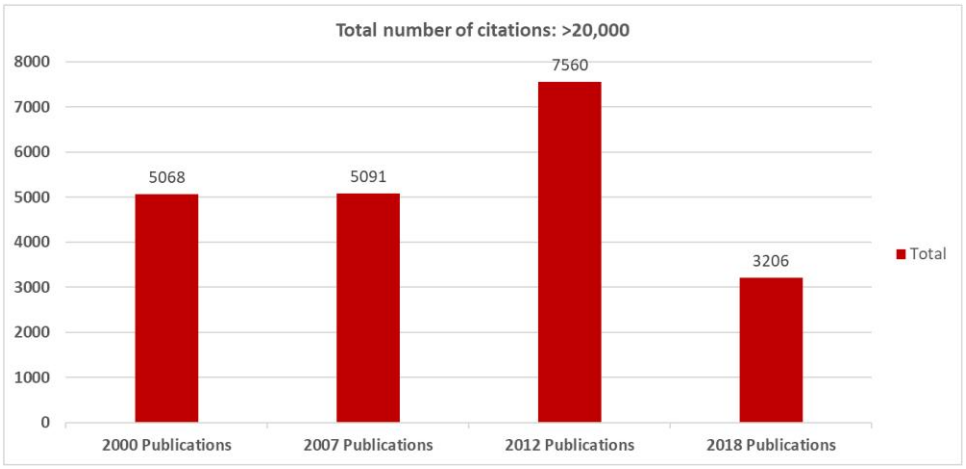

Figure 5 Universal definition of myocardial infarction—all publications. A graph showing that the universal definition of myocardial infarction documents have been cited over 20 000 times

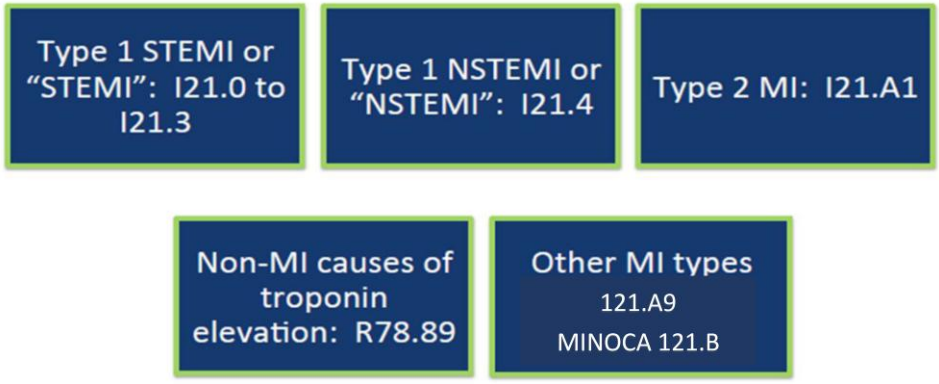
Type 1 STEMI or "STEMI": I21.0 to I21.3
Type 1 NSTEMI or "NSTEMI": I21.4
Type 2 MI: I21.A1
Non-MI causes of troponin elevation: R78.89
Other MI types
121.A9
MINOCA 121.B

Figure 6 New International Classification of Diseases ICD-10 diagnosis codes for MI on 10 January 2017.[15] In January 2017, the ICD codes were modified based on the universal definition of MI

made to the UDMI group, all of which were answered. The UDMI documents have been cited over 20 000 times (*Figure 5*).

International Classification of Diseases

In January 2017 the International Classification of Diseases (ICD) codes were modified based on the UDMI, i.e. Type-1 STEMI [121.0–121.3], Type-1 NSTEMI [121.4], Type-2 MI 121.A1, MI types 3–5 [121.A9],[15] and MI with non-obstructive coronary artery disease [MINOCA, 121.B] (*Figure 6*). This demonstrates the worldwide acceptance of the UDMI and its importance for patient care.

Importance of Type-2 myocardial infarction and criteria for diagnosis

Multiple registries and trials have shown that Type-2 MI is very common and the outcomes similar or worse than with Type-1 MIs.[16–20] In a study from Olmsted County, MN, the annual incidence of Type-1 MI decreased from 202 to 84 per 100 000 persons and Type-2 MI from 130 to 78 per 100 000 persons over 10 years.[21] This indicates that Type-2 MIs are a major health burden and data should be collected in epidemiological studies to define changes in the incidence of each type of MI.

Most Type-2 MIs have not only a demand function such as tachycardia or hypertension but have a clear coronary flow component as well. For example, tachycardia restricts diastolic time and hypertension, particularly with any endothelial dysfunction, results in coronary vasoconstriction and reduced coronary flow. Therefore, the idea that one can separate out as implied in the PRO argument those that are due to a primary coronary abnormality from those that are due to supply/demand imbalance misses the point that almost always there is a component of coronary flow insufficiency in Type-2 MIs.

Some trials have defined entry criteria on the basis of whether the patients randomized had a Type-1 or Type-2 MI,[9,11] and several trials including the NIH-funded ISCHAEMIA trial[22] have defined Type-2 MI as an outcome event.[9,22,23] In the ODYSSEY trial, in a

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prespecified analysis, the occurrence of Type-2 MI was reduced with lipid lowering by the PCSK9 inhibitor in patients with recent acute coronary syndrome (ACS).[23]

The diagnostic criteria for Type-2 MI are similar as for Type-1 in requiring a rise and/or fall of troponins with at least one value above the 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary atherothrombosis.

Proposal for a modest revision of the universal definition of myocardial infarction

A modest revision of the UDMI (*Figure 7*) has been proposed before[24,25] with shifting Type-2 MIs (SCAD, spasm, and coronary embolism) to Type-1 MIs. This mixing of pathophysiology and management is usually also not based on GDMT as with fibrinolysis and PCI for Type-1 MI. This proposal would impact on the ICD. These limitations are illustrated in *Figure 8*.

The PRO proposal maintains Type-2 MI in the classification but only has coronary-related as part of Type-2 MI (SCAD, spasm, and embolism) and moves non-coronary-related Type-2 MI and procedure-related MI to myocardial injury which violates the pathological definition of MI. Thus, moving many patients with a clear MI to a non-MI group.

Simply switching categories shouldn't change the management approach for type 2 MI. Of major concern is the effect that this proposal will have on confusion for patients and doctors and the impact on epidemiological data without improving patient care. Studies involving type-2 MI as defined in the UDMI have been reported in over 1100 manuscripts, all of which will now be irrelevant if a new definition is applied.

Furthermore, if this proposal were accepted, ICD codes would need to be changed, which the PRO group point out may take some time. It took the UDMI group almost 10 years to get the types of MI included during which time there will be confusion for patients, doctors, coders, and funding agencies.

The PRO side proposes to divide Type-2 MI, if it is maintained in the UDMI, into Type-2A and -2B based on whether CAD is present or not. There are now strong data that the presence of Type-2 MI with CAD is a more cardiovascular comorbid circumstance than a Type-2 MI in the absence of CAD. In a study of 93 patients with Type-2 MI,[17] only one-third had obstructive CAD indicating that CAD was a contributing factor in less than a third of patients. This illustrates the value of coronary angiography in identifying higher risk patients who could be targeted with high dose statin therapies. I therefore strongly support this proposal, but it requires a third category of 2C to account for those who do not undergo coronary angiography.

The future

With time there are going to be obligatory changes to the UDMI. What is important is that the weight of the evidence should be substantial to avoid trivial changes. The PRO argument clearly favours those very sophisticated centres who want to do angiography on most patients. A UDMI document must be useable by everyone, not just the most sophisticated sites and should include developing countries, countries at war, and rural areas such as outback Australia.

Additional objective criteria beyond the ECG criteria, already defined in the UDMI, are needed for ischaemia so that myocardial injury can be distinguished from MI. There is a need to define possible benefits of angiography and revascularization in Type-2 MI, and whether secondary prevention is beneficial in patients with CAD. Data is needed about how much myocardial injury is induced during uncomplicated PCI and CABG. Additionally, there is a need to define myocardial injury with trans-catheter valve intervention (aortic, mitral, and tricuspid), ablation, and non-cardiac surgery.

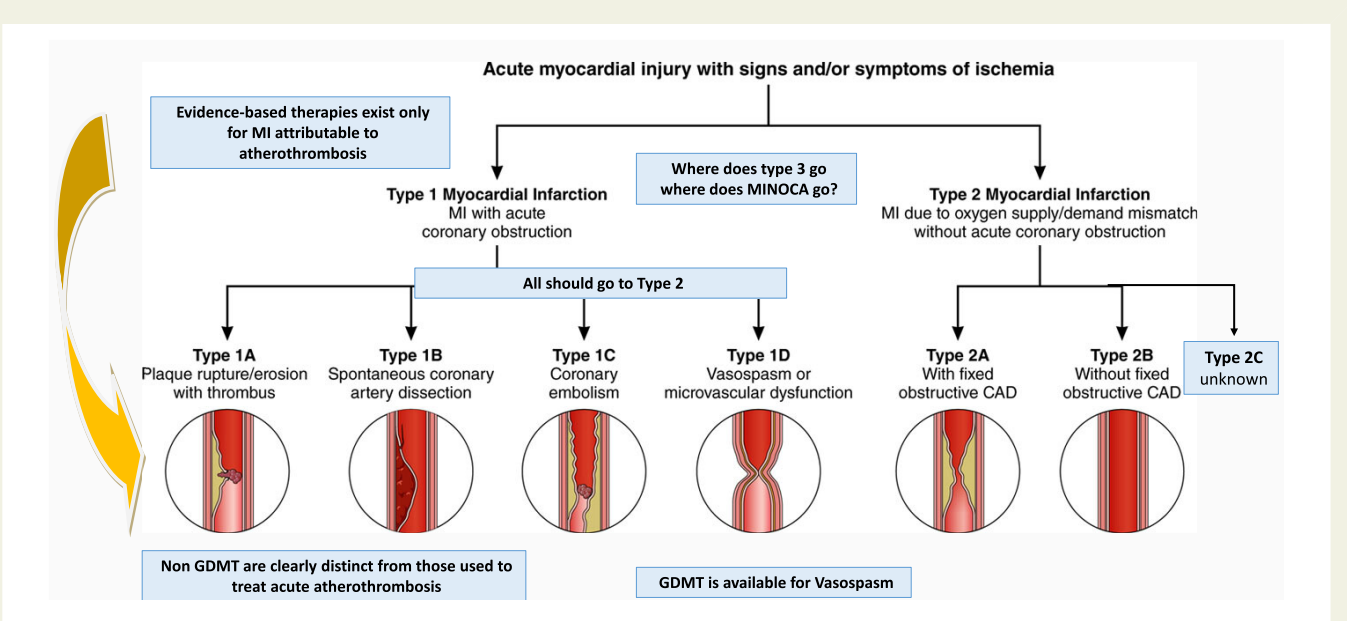
Acute myocardial injury with signs and/or symptoms of ischemia
Evidence-based therapies exist only for MI attributable to atherothrombosis
Where does type 3 go where does MINOCA go?
Type 1 Myocardial Infarction
MI with acute coronary obstruction
Type 2 Myocardial Infarction
MI due to oxygen supply/demand mismatch without acute coronary obstruction
All should go to Type 2
Type 1A
Plaque rupture/erosion with thrombus
Type 1B
Spontaneous coronary artery dissection
Type 1C
Coronary embolism
Type 1D
Vasospasm or microvascular dysfunction
Type 2A
With fixed obstructive CAD
Type 2B
Without fixed obstructive CAD
Type 2C
unknown
Non GDMT are clearly distinct from those used to treat acute atherothrombosis
GDMT is available for Vasospasm

Figure 7 Proposed modest revision to universal definition of myocardial infarction. The boxes define what should change in this proposal with guideline-directed medical therapy (GDMT) only existing for Type-1A MI and not for Type-1B and -1C. There is GDMT for vasospasm (Type-1D). These three types should remain as Type-2 MI as in the universal definition. There is no place in this proposal for MINOCA or type 3 MI

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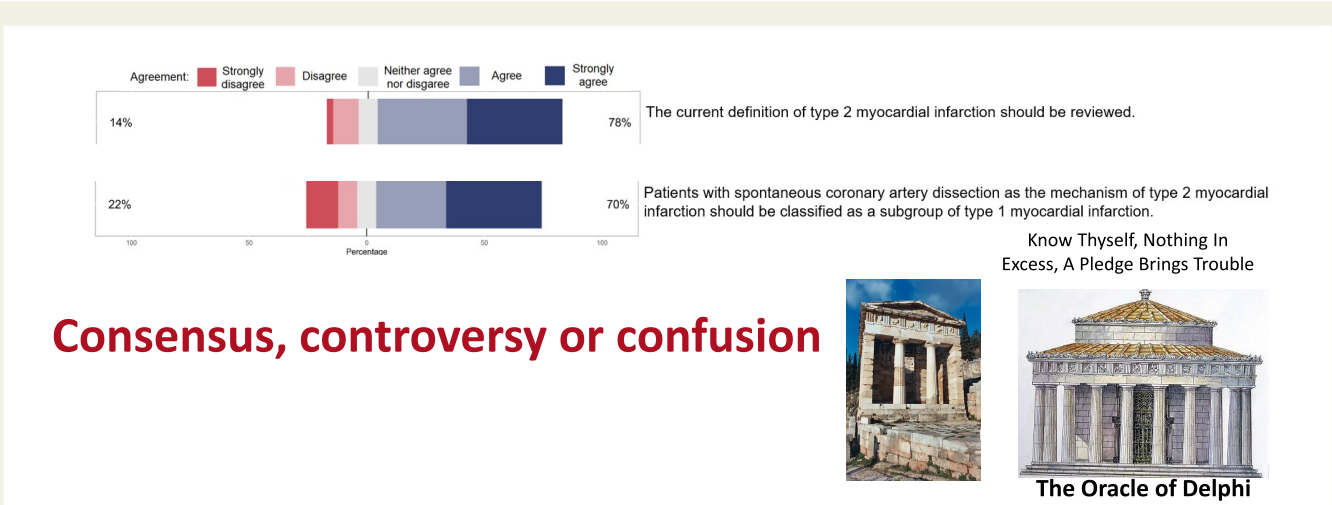

Figure 8 Consensus on the assessment and management of patients with Type-2 myocardial infarction: an International Delphi Study. In the International Delphi Study, 38 experts who had published on Type-2 MI were asked whether "the current definition of Type-2 MI should be revised"; 78% agreed and 14% disagreed with the others being uncertain. The second question asked was "whether SCAD as the mechanism of type 2 MI should be classified as a subgroup of type 1 MI"; 70% agreed and 22% disagreed, with the others being uncertain

The role of CTCA needs to be defined and whether MRI should be used as a criterion for the diagnosis of MI. Aborted MI is a subject worthy of discussion in the 5th UDMI.[26] Patient involvement in discussions to ensure patient focused outcomes and shared patient care should be done in any iterations of a new UDMI definition.

Conclusion

The definition of MI should be based on pathology and defined as myocardial cell death due to myocardial ischaemia. This definition needs to be preserved. The universal definition is not without blemish nor is it perfect, however, it should not be put to rest but rather needs careful revision.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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